

## Chapter 7: Achievements and limitations of cervical cytology screening

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### Abstract

This chapter reviews the contribution of cervical cytology, what makes it successful, the management of screen positives and how technological advances may affect its use in the future. Cervical screening has saved hundreds of thousands of lives but has not been available to women in the poorest countries. In countries where wide coverage has been achieved and quality assurance is in place, incidence and death rates have fallen by over 50% even though cervical cytology is logistically complex. The management of high-grade cervical intraepithelial neoplasia (CIN) is very effective, but low-grade cytological abnormalities require care to avoid over-treatment. The increasing rate of human papillomavirus (HPV) testing and the prospect of prophylactic vaccination will change the way cervical cytology is used, possibly giving way to HPV testing as the primary test in secondary prevention.

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### 1. Introduction

This monograph sets out to explore the role of HPV as the principal cause of cervical cancer, as well as the means of screening for it and ultimately, through vaccination, the means of preventing it. It is appropriate, therefore, to devote a chapter to reflect on the achievements of cervical cytology as the standard for secondary prevention that has been variably deployed in developed healthcare systems for 40 years. It is currently estimated that systematic screening can reduce death rates from cervical cancer by 70% or more. In the United Kingdom, this translates into at least 1000 lives per year among a population of 50 million [1,2]. It is also considered highly cost-effective. With an incidence beginning to rise in the late 20s and peaking in the mid 40s, loss of life years per cervical cancer case is often high, both as a mother and wife. When extended across North America,

Europe, Australasia and the Pacific Rim, the number of lives saved will have run into hundreds of thousands. Unfortunately, the benefits of screening have not been available to countries in the developing world due to a lack of resources, and this has been disastrous for women, with 80% of cervical cancer incidence and mortality occurring in these countries [3].

Treatment of pre-invasive lesions identified in screening programmes, has also enabled preservation of fertility, which is a crucial issue for many women, and, as a consequence, women around the world have developed great confidence in the “Pap Test” or “cervical smear”. Thus, any strategies to replace it will need to outperform it in terms of effectiveness, cost-effectiveness, safety and acceptability.

This chapter will review the successes and failures of cervical cytology from an epidemiological and clinical viewpoint and will touch on the psychosocial costs which some women endure. New technology has impacted on cytological techniques and has the potential to do so further in the near future.

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## 2. Pathogenesis of cervical cancer

Cervical cancer arises in the so-called transformation zone of the uterine cervix. This is the area which undergoes physiological metaplasia from glandular to squamous epithelium at the onset of adolescence. HPV infection is very common in young women after the onset of sexual activity, and when it persists, the viral oncoproteins produce perturbation of the cell-cycle controls, resulting in CIN. At their mildest (CIN-1), these lesions are generally no more than manifestations of HPV infection, but at their most severe (CIN-3), the risk of progression to cancer, if not detected and treated, is high. Fortunately, the transmission to cancer usually takes years, thus allowing the opportunity for detection by exfoliative cytology. The peak incidence of HPV infection occurs about age 20, the peak incidence/detection of CIN-3 occurs about age 30, and the peak incidence of cancer occurs in the 40s. It is estimated that without secondary prevention, cervical cancer would occur in around 1% of women who acquire an HPV infection, although for every cancer that occurs a far larger number of CIN lesions develop, of which the majority probably regress. Most of the pre-malignant and malignant lesions are of the squamous type but around 15% are of the glandular type. HPV types 16 and 18 are the dominant oncotypes in squamous lesions but type 18 is relatively more important in glandular lesions.

## 3. Public health considerations

Since the development of cytology-based cervical cancer screening using the Pap smear in the mid 20th century, Pap smears and new cytological technologies such as liquid-based cytology have been implemented for secondary prevention of cervical cancer. Although some have argued that there is no direct evidence of the impact of cytology screening on cervical cancer, such as evidence from a randomized clinical trial (RCT), there are overwhelming and convincing epidemiologic data to infer the impact of successfully implemented cytology screening on reducing cervical cancer rates.

Strong evidence for this comes from ecological correlations of incidence/mortality trends of cervical cancer with screening activities in populations, as reviewed recently [4]. In many high-resource countries, the implementation of a wide-coverage cytology program has led to concomitant reduction in cervical cancer incidence and mortality due to the detection and treatment of pre-cancerous lesions and earlier-stage, treatable cancers, respectively. Perhaps the best studied are the Nordic countries, where the trends in different countries have closely paralleled the population coverage of screening through organised programs. Incidence of cervical cancer has fallen by more than 50% in Finland, Sweden, Denmark and Iceland, where organised programs were initiated in the 1960s. In Denmark, greater reductions were observed in counties where screening was organised compared with counties where there was none. In contrast, rates

in Norway increased until the mid-1970s and then decreased, albeit slowly, due to opportunistic screening. The implementation of an organised Norwegian program in 1995 led to an immediate decrease in subsequent years, although the impact has been less than predicted from Finnish trends. Similarly, the rates of cervical cancer incidence in England were relatively constant, despite the presence of Pap smear screening, until the introduction of an organised program in 1988, which led to precipitous drops in rates in subsequent years. In the US, rates have also fallen by 75% or more since the 1960s, although rates remain high in regions typified by low resources as well as poor access and social/cultural barriers to screening. In Central and South America, coverage may be high in places, but the quality of the cytology programs and access to treatment are typically poor, and rates of cervical cancer remain some of the highest documented in the world.

Epidemiologic studies, especially cohort data, have also revealed the impact of cytology screening on reducing cervical cancer rates [4]. Large studies in the United Kingdom, Canada and Scandinavia have shown reductions in cervical cancer incidence in populations with cytology screening but the impact was highly variable, with efficacy ranging from 20% to 90%.

From a clinical performance viewpoint, cervical cytology is relatively insensitive for the detection of cervical pre-cancer and cancer and must be repeated frequently to achieve programmatic effectiveness. A meta-analysis [5] found that conventional cytology (positive threshold of low-grade squamous intraepithelial lesion) had a median sensitivity of 51% (range: 30–87%) for histologically confirmed CIN-2/3. Another recent overview of European and North American studies identified the sensitivity of cytology (threshold atypical squamous cells of undetermined significance (ASCUS) or equivalent) to be 53% (Fig. 1) [6]. This wide variability in sensitivity for detection of pre-cancer and cancer is likely attributable to the subjective nature of the cytological interpretation, which probably explains the widely variable impact of cytology on cancer rates observed in epidemiologic

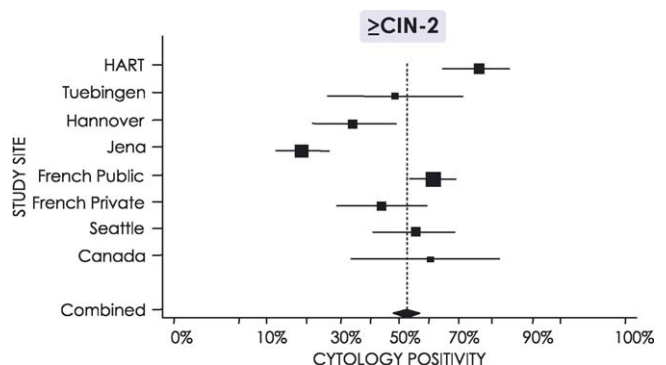


Fig. 1. Forest plot of sensitivity of cytology at the threshold of atypical squamous cells of undetermined significance (ASCUS) or greater to detect cervical intraepithelial neoplasia (CIN) 2 or greater, reported from several European cytology laboratories. Reprinted from [6] with permission from Wiley.

studies. To achieve high sensitivity of detection, cytology reporting must include “borderline” or uncertain abnormalities, which can lead to over-referral to colposcopy and potentially over-treatment. The success of even well-established cytology programs in detecting cervical pre-cancer and treatable cancer is partly attributable to repeated screening of women during the relatively slow progression from incident HPV infection to pre-cancer (typically 2–15 years) and from pre-cancer to cancer (typically 10 or more years).

The successes of cytology programs in reducing the burden of cervical cancer in selected countries and regions must be juxtaposed with rising global rates of cervical cancer incidence and cancer-related mortality [3]. Thus, it is important to recognise the limitations of cytology-based programs, which arguably have reached their maximum impact for global cervical cancer prevention. First, as described above, cytology has limited sensitivity for the detection of pre-cancerous lesions and treatable cancers. Thus, repeated cytology over short intervals (annual, biennial and triennial) has been used to achieve program efficacy; only repeatedly normal cytology denotes safety and permits safe lengthening of screening intervals. Second, cytology is poorly reproducible, with poor agreement even among experts in quality-controlled programs [7]. Cytology is a subjective test, and in programs without quality control/quality assurance, it is virtually impossible to achieve and maintain the clinical performance of cytology. The US National Cancer Institute’s experience in Guanacaste, Costa Rica, where Pap smears were used ineffectively, was that it took many years to establish a high-quality cytology program that approached US standards. Third, cytology is labour intensive, and, to date, has been refractory to high-throughput automated screening (see below). Fourth, despite the low cost of consumables and because of the three reasons cited above, high-quality cytology is expensive in absolute terms and may not necessarily be the most cost-effective option for screening [8]. Not surprisingly, excess cervical cancer mortality in the US regions and elsewhere is considered a signpost of health disparities and low socioeconomic status.

We must continue to recognise both the strengths and limitations of cytology for cervical cancer screening; in populations vaccinated against HPV-16 and -18 we should anticipate that the positive predictive value of cervical screening will be reduced because there will be fewer high-grade lesions among women with cytological abnormalities (see chapter 20). It is therefore rational to develop multiple, viable modalities for cervical cancer prevention, including methods that achieve similar or better screening performance than cytology alone but also meet the demands of underserved populations, such as low cost, fewer than three visits (cytology, colposcopy and treatment) for an intervention (screening) cycle and/or fewer interventions in a lifetime due to a greater negative reassurance of a single intervention. It is naïve to think that one modality, whether it be cytology-based screening, visual inspection by acetic acid, HPV-DNA testing or HPV vaccination, will meet the demands of all populations throughout

the world. Importantly, each screening method must be validated for its technical performance and must be cost-effective within the capacity of the region in which it is to be adopted. In other words, the cost-utility of one method versus another must be evaluated within the limits of acceptable expenditures and available resources. Given the cultural, social and religious diversity globally, it is an unrealistic expectation that there is, or will ever be, a “one size fits all” global cervical cancer prevention strategy.

#### 4. What makes a screening programme work?

When viewed from the perspective of a population as opposed to that of an individual woman, there are a number of key considerations which come into play when assessing why programmes work. Insight can be gained from the UK screening programme, which was launched in the late 1980s after 20 years of essentially opportunistic activity. Between 1988 and 1995, the incidence fell by 40% (Fig. 2) and by 2004 the death rate from cervical cancer had fallen by almost 50% [9]. The key to this success lay in a systematic call/recall programme where every woman in the screening age range received regular invitations. This was backed up by the establishment of a quality assured programme which addressed every stage of the process, from smear takers, to laboratory reading, to colposcopic management. A multidisciplinary approach involving gynaecologists, family practitioners, nurses and cytopathologists is key, backed up by an administrative infrastructure to track women through the process. Training is accredited at every stage and accreditation is ongoing, as are the development and adherence to clinical practice guidelines. Performance indicators are systematically obtained from every laboratory and colposcopy clinic. Family practices, which are the backbone of the smear taking service, receive additional payment for achieving a coverage threshold of 80%. Finally, the whole programme is highly valued by women and there is considerable political support, which ensures adequate funding, including evidence-based advances. In the absence of this degree of rigour and attention

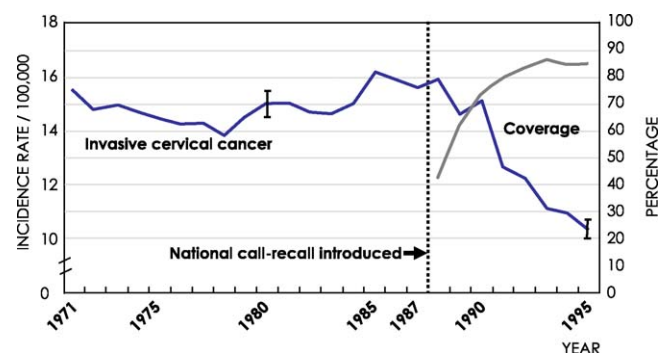


Fig. 2. Age-standardised incidence of invasive cervical cancer and coverage of screening: England, 1971–1995. Reprinted from [35] with permission from BMJ Publishing Group.

to detail, cervical screening will not only be less successful but risks doing more harm than good; for example, young women at low risk of cancer but at risk of over-treatment for low-grade abnormalities.

## 5. The management of screen positives

### 5.1. Overview

The management of screen positives has been a crucial element in the success of cervical screening. The challenge has always been to ensure that the benefits of treating women who are found through colposcopic examination to have CIN outweigh the risks of treatment. There is, of course, a spectrum in this benefit/harm balance. While excision of CIN-3 is mandatory by most, destructive treatment is still used by some. Aggressive treatment in women with CIN-1 risks doing more harm than good, and this issue has been highlighted recently by a systematic review which indicates that excisional treatment for CIN is associated with an increased risk of premature labour, indicating membrane rupture [10] (see chapter 9). Treatment for CIN now most popularly involves colposcopically controlled excision of CIN using diathermy loop excision LEEP (loop electrosurgical excision procedure) or LLETZ (large-loop excision of the transformation zone) or ablation by cryotherapy or diathermy, all of which are associated with less morbidity and cervical scarring than the classic cold-knife cone biopsy. The principal risk factor for treatment failure is involvement of the excision margin with CIN, although HPV positivity following treatment, as an indicator of incomplete excision, has recently been shown to be the strongest predictor of persistent disease. Long-term follow-up studies have indicated that an increased risk of invasive disease persists for at least 10 years following treatment of CIN. This necessitates follow-up cytology, which is usually annual for between 5 and 10 years before returning to routine recall. A number of studies over the past 5–10 years have indicated clearly that if an HPV test is negative 6 months following treatment the risk of treatment failure is so low that intensive follow-up can be disregarded and women can be returned to a normal recall protocol (see chapter 9). The current approach to the management of abnormal cytology is now considered in more detail.

### 5.2. Evolution of treatment for CIN

Prior to the advent of colposcopy, the response to abnormal cytology was a cone biopsy, which was considered both diagnostic and therapeutic for CIN. Colposcopy promoted the development of office or outpatient treatment procedures for CIN as both the grade and the location of these lesions could now be documented prior to selecting therapy. Laser ablation supplanted cryotherapy and diathermy in the 1980s, only to give way in the next decade to the less-expensive and less technically challenging office excisional procedures

LEEP and LLETZ. All these procedures have been shown in randomised trials to have essentially similar clearance rates [11,12]. The failure rate for all cervical procedures has been shown to be related more to the size of the lesion and less to the histological grade. Despite high success rates for all modalities (90–95%), the rate of invasive cervical or vaginal cancer following treatment for CIN has been shown to be at least 2.8-times that of the population at large for up to 20 years following treatment [13]. Therefore, regular attendance for follow-up is critical for women post-treatment if they are to achieve the maximum protection by detecting residual or recurrent disease at a treatable stage.

During the first 20 years following the introduction of colposcopy and office out-patient treatment options for CIN, treatment of minor low-grade lesions (CIN-1) became as established in the US as treatment of high-grade lesions (CIN-2/3). This occurred, in part, because of the widespread availability of low-cost office treatment modalities such as cryotherapy and LEEP, and also because of the perception that the CIN spectrum was one of progression from CIN-1 to CIN-2 to CIN-3, and eventually to invasive cervical cancer. Therefore, all grades of CIN were deemed appropriate for treatment in order to prevent the expected risk of progression. Increasing recognition that the CIN spectrum is not one of progression of low- to high-grade and that only high-grade CIN, particularly CIN-3/carcinoma *in situ*, is a true pre-cancer, fostered the 2001 American Society for Colposcopy and Cervical Pathology (ASCCP) Consensus Guidelines [14] and those used in the UK Cervical Screening Programme [15]; the “preferred” management of women with CIN-1 is expectant management without treatment, as at least 70% of these lesions will resolve spontaneously and there will still be plenty of time to detect and treat the other 30% while still benign. The 2005 American College of Obstetricians and Gynecologists (ACOG) guidelines on the management of women with abnormal cervical cytology affirmed this approach [16].

### 5.3. New cytological terminology, new challenges

In 1988, the cytological classification system called The Bethesda System (TBS) replaced the old Papanicolaou Classification in the US, and this system has subsequently been adopted in many countries around the world. TBS combines koilocytotic atypia and mild dysplasia (CIN-1) into the single category of low-grade squamous intraepithelial lesion (LSIL). More importantly, it designates that atypia not reliably designated as within normal limits but not definitely abnormal should be placed in the new category of atypical squamous cells of undetermined significance (ASCUS). The inclusion of atypical cell changes in the abnormal Pap test categories changed traditional colposcopic triage guidelines and more than doubled the referral rate to colposcopy from that when the threshold for colposcopy began with dysplasia or mild dyskaryosis. In the US and UK, these two categories account annually for approximately 6–8% of the Pap results



given to women participating in routine cervical cytological screening. A successful screening program can benefit from the efficient triage of this large number of women into differential risk categories for appropriate management and treatment.

A significant consequence of the lowered cytological threshold for referral to colposcopy is the increased difficulty that colposcopists now often have in detecting early, small high-grade lesions than their predecessors, who had to respond only to markedly abnormal cervical cytology that carried a high probability of finding often large CIN-2/3 lesions. A number of studies, including the US National Cancer Institute-sponsored ASCUS/LSIL Triage Study (ALTS) have demonstrated that colposcopy misses about one-third of high-grade lesions in women with concurrent low-grade cytological abnormalities. Furthermore, colposcopy only detected 70% of these missed CIN-2/3 abnormalities during 2-year follow-up of a biopsy of an apparent low-grade lesion [17,18].

#### 5.4. *Current protocols for managing abnormal cytology*

Management of abnormal cervical cytology revolved, until recently, around either immediate referral to colposcopy or triage to colposcopy only when cytology was again abnormal on a program of accelerated repeat. The choice of management was determined primarily by the degree of abnormality of the screening cytology. Referral to colposcopy is universally accepted for high-grade cytology, but for 20 years the management of low-grade abnormalities (ASCUS/LSIL) has been argued about. Evidence from clinical trials has indicated that testing for high-risk HPV can usually triage women to immediate colposcopy or further cytological surveillance [19–21]. US and UK guidelines recommend colposcopy as the initial management for all women with any cytological interpretation of atypical squamous cells “cannot rule out high grade” (ASC-H), atypical glandular cells (AGC), LSIL and high-grade squamous intraepithelial lesion (HSIL). Women with ASCUS may be managed by cytology or HPV triage. The management of women who have equivocal or borderline cytology (low-grade cytology, i.e. LSIL is not HPV tested) who test negative with HPV could involve repeat cytology at 12 months and, if negative or still HPV-negative, return to routine recall interval. The exact protocol will depend on the clinical guidelines developed nationally. Follow-up after treatment of CIN has traditionally involved repeat annual cytology, although it is now clear that HPV testing can distinguish those women who are at risk of treatment failure and who require closer surveillance from those who are at very low risk and can be safely returned to routine recall more powerfully than cytology.

#### 5.5. *Psychosocial consequences of cervical screening*

The anxiety experienced by many women when they have a cervical screening test is both well documented in the liter-

ature and widely acknowledged by those who care for these women. For some women, it is fear that they have, or may be found to have cancer which engenders anxiety; for others, depression, anger and the sort of stigma associated with sexually transmitted infection are all psychosocial factors [22]. This latter issue has been emphasised recently in a study which has addressed the impact of HPV-positive testing on women undergoing screening [23].

Compared with women who receive a normal result, women who receive results of a mild abnormality have elevated anxiety levels and those referred for colposcopy have still higher levels [24]. Following colposcopy, anxiety levels tend to fall and, indeed, those kept under cytological surveillance experience less anxiety over time [25]. Women with ASCUS/LSIL results have been studied in a number of settings. In a randomised trial where women with ASCUS/LSIL had the opportunity to choose either colposcopy or surveillance, there was no psychosocial benefit compared with those who underwent surveillance, and anxiety levels again fall in both arms over time [25]. In another study of women with ASCUS/LSIL who experienced HPV triage, those who were HPV positive were more anxious than those who were HPV negative; they were also more anxious than an equivalent group who had not experienced HPV testing [26]. Many women have a poor understanding of cervical screening and it has been shown that improving communication with women can ameliorate anxiety [27]. Considerable efforts have been made to improve information access, with the aim of not only reducing anxiety but also being more honest about the benefits and limitations of cytology. HPV testing, which is going to play an increasing role in cervical screening, presents a new set of challenges for both women and their partners in terms of education and understanding.

#### 5.6. *Management of screen-positives in the future*

The traditional cervical cancer prevention strategy – detection and treatment of cervical cytology and histological changes – is being replaced by one in which the focus of prevention is turning towards detection of, and vaccination against, the causative agent (HPV). It is therefore likely that current management algorithms will change for the following reasons: (1) there is increasing evidence that detection of HPV types 16 and 18 may be a more specific triage for equivocal and low-grade cytological abnormalities and for post-colposcopy management [28,29] (Fig. 3); (2) high-risk HPV detection may become the primary screening test, followed by either cytological or type-specific HPV testing for triage of positive tests [28] (Fig. 4); (3) HPV vaccines will have a significant impact on the rate and distribution of abnormal cytology results and potentially reduce the commitment to screening and secondary prevention that has so successfully served us to this point. If we are to continue to achieve high success in the prevention of cervical cancer we must commit to continued diligence in providing cervical

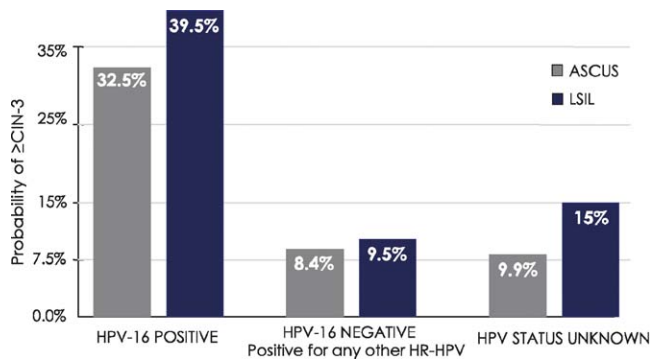


Fig. 3. Probability of cervical intraepithelial neoplasia (CIN)-3 or greater over a 2-year period for atypical squamous cells of undetermined significance (ASCUS) and low-grade squamous intraepithelial lesions (LSIL) by HPV type. In the ALTS trial, the risk of an LSIL Pap without knowledge of HPV type for prediction of the detection of CIN-3 or greater over a period of 2 years was less than half the risk noted for LSIL testing positive for HPV-16, and the risk for ASC-US was tripled when HPV-16 was detected. In contrast, the risk for ASCUS or LSIL positive for any other high-risk type was substantially less, indicating that type-specific testing for 16 and 18 may become an important part of risk stratification and future management strategy, particularly in post-colposcopy follow-up and expectant management of CIN-1. Reprinted from [28] with permission from Oxford University Press.

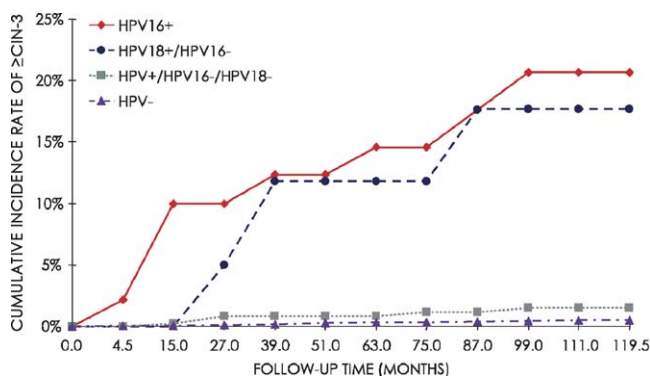


Fig. 4. The cumulative incidence of cervical intraepithelial neoplasia (CIN)-3 or greater over a 10-year period in women ages 30 and older as a function of a single HPV test result at enrolment. HPV testing for high-risk HPV types was by Hybrid Capture 2. Reprinted from [29] with permission from Oxford University Press.

cancer prevention services that incorporate both HPV vaccination and continued screening in whatever form, as well as diligent management of screen-positives (see chapters 9 and 20).

## 6. Technology in cervical cytology

The Pap test has survived virtually unchanged for 50 years, a testimony to its efficacy. During the last 10 years, however, two technological advances have come to the forefront. The first of these is liquid-based cytology (LBC) where, instead of spreading the exfoliate, obtained with a spatula, onto a glass slide and fixing, the exfoliate is stirred immediately into a pot

containing a preservative and, on receipt at the laboratory, the cells are aspirated onto a filter and similarly stained on a glass slide. The two qualitative differences are that:

- the slide has a more homogeneously spread cell preparation without clumping and obscuring by white cells, and
- the liquid residue can be used for further testing, such as HPV, without requiring another clinical specimen.

Claims have been made that LBC is more sensitive than conventional cytology, and although this has been refuted in a recent systematic review [30], much of the primary research underpinning this review had methodological weaknesses. In a large real-life UK pilot study involving 100,000 women, LBC was shown to reduce inadequate slides by 80%, thereby requiring far fewer women to re-attend and increasing laboratory throughput [31]. It was also reported to be cost effective, a decision which was supported by NICE, who recommended national implementation [32]. LBC has become the method of choice in the US and the UK. Co-testing for HPV concurrent with cytology would, because of increased sensitivity, obfuscate any potential sensitivity advantage of LBC versus Pap smears [33]. The convenience of LBC (single collection for both cytology and HPV-DNA testing), which enables reflex testing following an ASCUS result, should be weighed against its added cost as compared with the Pap smear.

The second technological development of significance in cytology is automation, in which computer technology using algorithms of recognition can identify the most abnormal areas of an entire slide and present them for the purpose of reading. In addition to this facility, it is possible for computerised ranking of the slide in terms of abnormality, with the least abnormal (i.e. normal) to be reserved for no further review, meaning no human reading is required. This technology has been around for some time but has never been subjected to sufficiently rigorous trials to provide evidence of the extent of any benefit or its cost-effectiveness that would justify its wider implementation. A recent systematic review [34] and modelling exercise commissioned by the UK Health Technology Assessment Programme concluded that insufficient evidence existed to be able to recommend use of automated cytology. A large trial has been established in the UK (HTA, [www.ncchta.org](http://www.ncchta.org)) to compare manual and automated reading using two approved systems, Imager™ (Cytoc) and FocalPoint™ (Tripath), which will report in 2009. Clearly, automation has the potential to achieve efficiency gains and possibly increase diagnostic accuracy.

While morphological cytology will continue to be the test to determine the need for further investigation, it may be replaced as an initial screen by HPV testing, the evidence for which is described in chapter 10. Technological advances offer the opportunity to achieve at the very least efficiency gains, and possibly enhance performance in terms of detection.

## 7. Conclusions

Cervical screening works but there are some major challenges ahead. The most significant is that most women in the world have been denied any form of prevention, which, if continued, will result in a million deaths from this disease over the next 5 years. If this situation is to change there has to be a new approach, such as a strategy of primary prevention, a possibility offered by vaccination. Otherwise, affordable, cost-effective strategies of secondary prevention, which are feasible in low-resource settings, need to be implemented. These are in development in a number of areas in the world (see chapter 8), although evidence of benefit in terms of reducing deaths will take at least 5 years to accrue.

With regard to developed settings with cytology programmes in place, challenges remain in the management of low-grade abnormalities, which are expensive and troublesome for women. New approaches using HPV testing to complement, or even replace cytology as an initial screen, may ameliorate this situation, although many women at low risk will still require colposcopy or less invasive treatment for HPV infection.

LBC assists adjunctive testing and can achieve greater laboratory efficiency by reducing inadequate slides and increasing throughput. Automated testing on liquid-based samples may also be demonstrable as a means of maintaining or even increasing diagnostic accuracy while at the same time achieving efficiencies within the laboratory, thereby requiring less labour intensive effort to maintain efficacy.

Other biotechnological advances such as electro-optical devices and molecular markers may be capable of replacing cytology in time, but for the immediate future cervical cytology will remain the standard means of providing protection for women at risk of developing cervical cancer. There are financial and psychological costs to screening, although compared with many other disease prevention strategies cervical screening is both acceptable and highly cost-effective.

## Disclosed potential conflicts of interest

HCK: Consultant (GlaxoSmithKline)

JTC: Consultant (Digene Corporation, GlaxoSmithKline, 3M Pharmaceuticals); Speakers Bureau (Digene Corporation, 3M Pharmaceuticals); Data and Safety Monitoring Board (Merck and Co., Inc.)

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